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(54) Inclusion complexes of steroids with δ-cyclodextrin

(57) The title complexes have 3-100 times the water-solubility of the uncomplexed steroids, e.g. spironolactone, nortestosterone, methyltestosterone, androst - 4 - ene - 3, 17 - dione, progesterone, Reichstein S, Reichstein S aceate, 16α - methyl - Reichstein S, Hydrocortisone, estrone, dexamethasone, prednisolone, triamcinolone, pregnenetriolone triacetate.

Pharmaceutical compositions containing the title complexes are free from the nephrotoxic effects of the corresponding α- and β-cyclodextrin complexes owing to the faster enzymatic decomposition of δ-cyclodextrin.

ERRATUM

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Front page, heading (56) Documents cited *for* δ-cyclodextrin (first and second occurence) *read* γ-cyclodextrin
Front page, heading (54) Abstract title *for* δ-cyclodextrin *read* γ-cyclodextrin
Front page, heading (57) Abstract *for* δ-cyclodextrin *read* γ-cyclodextrin

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SPECIFICATION

Inclusion complexes of steroids with γ-cyclodextrin

The invention relates to the inclusion complexes of steroids poorly soluble in water with γ-cyclodextrin, to a process for their preparation and pharmaceutical compositions containing them as active ingredient.

Cyclodextrins are formed from starch by the cyclodextrin transglycolase enzyme. The cyclodextrin molecules consist of 6, 7 or 8 glucopyranose unit forming α-1,4-glucose units. Structurally they are characterized by a special arrangement of the hydroxyl groups. All the secondary hydroxyls are situated on one edge of the ring, while all the primary hydroxyls are placed on the other edge of that ring. Therefore the outer surface of the ring is essentially hydrophilic which ensures that the cyclodextrins are water-soluble. On the other hand the inner surface of the rings has a hydrophobic character since in that part of the molecule only hydrogen atoms and glucosidal oxygen bridges are to be found. Consequently, apolar molecules of appropriate shape and size penetrate into the cave inside the cyclodextrin and form cyclodextrin inclusion complexes, which may be isolated in a microcrystalline form.

The physical and chemical stability of the guest molecules is essentially improved by the formation of inclusion complexes and in numerous cases it has bee observed that this results in an increase in the solubility as well.

With respect to α-cyclodextrin the following solubility increasing effects have been published: Lautsch, Rauchut, Grimm and Broeser [Z. Naturforsch., *12.b*, 307-314 [1957]] described that the solubility of acetylene in an aqueous α-cyclodextrin solution increases to 1.2-times its original value; according to Cohen and Lach [J. Pharm. Sci., *52*, 132-136 [1963]] the solubility of hydroxybenzoic acids and parabenes is increased to 1.25 to 6-times the original values; Lach and Cohen [J. Pharm. Sci., *52*, 137 [1963]] observed in the case of 11 structurally different compounds a 1.1 to 3.4-times increase in solubility in an aqueous α-cyclodextrin solution; according to Lach and Chin [J. Pharm. Sci., *53*, 69-73 [1964]] for substituted benzoic acids the increase was 1.1 to 10-fold; Uekama, Hirayama, Matsuo and Koinuma [Chem. Lett., *1978*, 703-706] reported that the solubility of tolbutamide in an α-cyclodextrin solution increases to twice of the original value; Uekama and Hirayame [Chem. Bull., *26*, 1195-1200 [1978]] published a 2.8-times solubility increase for prostaglandin - F_2 - alpha while according to Yamada, Inaba and Ikeda [J. Pharm. Sci., *68*, 1059 [1979]] in case of prostaglandin - E_1 methyl esters a 27.5-times solubility increase was achieved by using α-cyclodextrin.

β-Cyclodextrin has also been reported to possess analogous properties. For example Lautsch, Bandel and Broeser [Z. Naturforsch., *11b*, 282-291] increased the solubility of an azo-dye to 6 times the original value; Cohen and Lach [J. Pharm. Sci. *52*, 132-136 [1963]] achieved a 1.1 to 2-times solubility increase in case of hydrobenzoic acids and parabenes; Lach and Cohen [J. Pharm. Sci., *52*, 137 [1963]] reported a 1.03 to 3.6-times solubility increase for various, structurally different compounds in the presence of β-cyclodextrin; according to Lach and Chin [J. Pharm. Sci., *53*, 924-927 [1964]] the solubility of benzocaine was increased to twice its original value; Thakkar, Kuehn, Perrin and Wilham [J. Pharm. Sci., *61*, 1841-1843 [1972]] reported a 1.3 to 3.3-times solubility increase for barbitals; Uekama, Matsuo, Hirayama, Yamaguchi, Imamura and Ichibagase [Chem. Pharm. Bull., *27*, 398-402 [1972]] observed a 3-fold solubility increase for acetohexamide; according to Uekama and Otagiri [Chem. Pharm. Bull., *23*, 201-208 [1975]] the solubility of flufenamic acid could be increased by β-cyclodextrin by a factor of 6.6; according to Uekama, Hirayama, Matsuo and Koinuma [Chem. Lett., *1978*, 703-706] in a β-cyclodextrin solution the solubility of tolbutamide can be increased by a factor of 2.75; Frank and Cho [J. Pharm. Sci., *67*, 1665-1668 [1978]] could increase the solubility of prostaglandin-E_2 to four times its original level; Uekama and Hirayama [Chem. Bull., *26* 1195-1200 [1978]] increased the solubility of prostaglandin - F_2 - alpha by a factor of 3.8; Uekama, Hirayama, Yamada, Inaba and Ikeda [J. Phar. Sci., *68*, 1059 [1979]] reported that the solubility of prostaglandin - E_1 - methyl esters in water could be increased by a factor of 7.5; Pauli and Lach [J. Pharm. Sci., *54*, 1745-1750 [1965]] increased the solubility of seven different aromatic carboxylic acids in an aqueous β-cyclodextrin solution by a factor of 1.05 to 4.2.

Of the steroids only testosterone and cortisone acetate has been tested [Lach and Pauli, J. Pharm. Sci., *55*, 32-38 [1966]] and a 2.7 and 4.3 times increase, respectively was observed in the water-solubility in the presence of β-cyclodextrin.

Testing the effect of γ-cyclodextrin on the water-solubility of various steroids we observed surprisingly high increases. In relatively dilute [several percentage] γ-cyclodextrin solutions the water-solubility of various steroids was increased by about a factor of 3 to 100, generally 3.4 to 66.

In this way injectable steroid solutions can easily be prepared. Hereinbelow we list the saturation concentrations of aqueous γ-cyclodextrin solutions of several steroidal compounds:

methyltestosterone	7.5 mg./ml.
spironolactone	3.0 mg./ml.
hydrocortisone	5.0 mg./ml
prednisolone	8.2 mg./ml.
dexamethasone	6.0 mg./ml.
triamicinolone	14.6 mg./ml.

These compounds could hitherto be applied as oily, intramuscular injections, of organix solutions where there was always a danger of toxicity, or their water-soluble derivatives had to be prepared. By forming γ-cyclodextrin complexes of these and other steroidal compounds injectable aqueous solutions can be prepared without any difficulty.

A further essential advantage of γ-cyclodextrin complexes over the inclusion complexes with α- or β-cyclodextrin is that the enzymatic decomposition of α- and β-cyclodextrin is very slow, therefore they have a nephorotoxic effect when administered

parenterally. Therefore from α- and β-cyclodextrin complexes of steroids could not be prepared injectable compositions even if their solubility increasing effect were satisfactory. On the other hand, β-cyclodextrin has such a flexible molecular structure that the rate of its enzymatic decomposition is about 100 times higher than that of β-cyclodextrin; accordingly, the cyclodextrin ring is quickly split in the living organism and is metabolized just as starch or linear cyclodextrins which are essential components of human foods. Therefore, when γ-cyclodextrins are administered parenterally, the danger of toxicity can practically be neglected.

Also the absorption of orally or locally administered steroids can effectively be increased by γ-cyclodextrin.

The inclusion complexes of steroids with γ-cyclodextrin have a hydrophilic character, they moisten with water immediately and the steroids do not float on the surface of the water. The saturation concentration is achieved quicker, generally by an order of magnitude, than without γ-cyclodextrin and the saturation concentration is about 10 to 100-times higher than that of the steroids alone.

The invention relates to the inclusion complexes of steroids poorly soluble in water with γ-cyclodextrin. In this context the term "steroids poorly soluble in water" is used to relate to steroidal compounds, which are insoluble in water or have, for practical purposes an unsuitably low water-solubility. As a result of forming inclusion complexes with γ-cyclodextrin the steroids poorly soluble in water and having a hydrophobic character become more hydrophilic, hence both the rate of dissolution and the saturation concentration increase by 1 to 2 orders of magnitude; accordingly the biological applicability of the compounds is improved.

Cyclodextrin inclusion complexes can be prepared in several differnt ways. For example the cyclodextrins can be kneaded with the compounds to be included in the presence of a small amount of water; or an organic solution of the compounds to be complexed may be shaken with an aqueous cyclodextrin solution; or the desired inclusion complexes can be prepared by coprecipitation from a common homogenous solution of the two components. In the case of steroids complexes of satisfactory quality can be prepared by the latter procedure.

According to another aspect of the invention there is provided a process for the preparation of inclusion complexes of steroids poorly soluble in water with γ-cyclodextrin. According to this procedure a solution of the steroids in an alkanol containing one to 3 carbon atoms, ether or acetone is admixed with an aqueous solution of γ-cyclodextrin between room temperature and the boiling point of the solvent employed, the mixture is cooled and the precipitated steroid-γ-cyclodextrin complex is isolated.

According to a preferred embodiment of the above procedure an aqueous γ-cyclodextrin solution is prepared at a temperature of 50 to 70°C, the steroid is dissolved in an equal volume of a 96% by vol. ethanol solution at the same temperature and the two solutions are admixed. Under these conditions at 50 to 70°C a homogeneous solution is formed, which is then cooled to room temperature under vigorous stirring in 3 hours. By cooling the precipitation of the crystals of the inclusion complex is initiated. To complete the procedure the mixture is kept at a temperature of 0°C for additional 12 hours. The precipitated product is filtered off or separated from the mother liquor by centrifuging, whereupon it is dried at 80°C under atmospheric pressure or at 40°C *in vacuo*.

Solutions can be prepared also by admixing the steroids with a 1 to 10% by weight, preferably 3 to 5% by weight aqueous solution of γ-cyclodextrin. Thus injectable solutions are prepared. This process is a further subject of the present invention.

The steroids may generally be complexed with γ-cyclodextrin to form inclusion complexes efficiently by using two or more moles of γ-cyclodextrin per mole of steroid.

If the steroid is used in a higher proportion, it is only partially included in the γ-cyclodextrin molecules.

To summarise, the conversion of steroids to complexes with γ-cyclodextrin has the following advantages:

a/ Aqueous [injectable] solutions having considerably higher steroid concentration than before can be prepared.

b/ α-Cyclodextrin has an about two orders of magnitude better enzymatic metabolization than either - or β-cyclodextrin, hence it can be administered parenterally.

c/ The inclusion complexes of steroids with γ-cyclodextrin moisten quickly and efficiently with water, the velocity of their dissolution and frequently even the saturation concentration is improved by orders of magnitude [powder ampoule injections can be prepared], therefore in case of tablets or ointments a quicker and better absorption is expected.

According to a still further aspect of the invention there are provided pharmaceutical compositions containing the inclusion complexes of steroids poorly soluble in water with γ-cyclodextrin. The pharmaceutical compositions comprise the inclusion complexes optionally in association with conventional carriers, excipients and optionally further conventional additives and can be prepared by generally known techniques for the preparation of pharmaceutical formulations.

The invention will now be illustrated in greater detail by the following specific Examples, which are given for illustration and not limitation of the invention. In the Examples the ratios given for the complexes are molar ratios and the percentages, if not otherwise stated, are by weight.

Example 1

The preparation of aqueous steroidal solutions

Various steroids where shaken in α-cyclodextrin solutions of various concentrations at 25°C for 3 hours. The steroids were always employed in an excess amount, i. . at the end of the experiments there was some solid steroid in the solution. After filtering off this solid the dissolved steroid amount was determined. As shown in Tables I-VII the solubil-

ity does not show a continuous increase as a function of the γ-cyclodextrin concentration but a more or less sharp maximum can be observed. Depending on the steroid there is a narrower or broader γ-cyclodextrin concentration range in which the increase of solubility is the greatest. Exceeding this optimum range the solubility of the steroid starts decreasing again but still remains considerably higher than without γ-cyclodextrin.

Tables I-VII illustrate the dependence of the water-solubility of various steroids on the concentration of γ-cyclodextrin.

According to the data set forth in Tables I-VII a maximum water-solubility can be achieved in a 3 to 5% γ-cyclodextrin solution. In order to compare the increase in the solubility of various steroids said compounds were shaken in a 10% [i.e. 7.51×10^{-2} moles/lit.] γ-cyclodextrin solution at 25°C for 3 hours, whereupon the quantity of the dissolved steroids was determined. The results are given in Table VIII.

Table I

Solubility/s of methyltestosterone as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	Dissolved methyltestosterone mg./ml.	moles/lit.	S/S$_o$
0	0	[S$_o$ = 0.070	$2.35 \cdot 10^{-4}$].	1
1.58	0.0093	3.2	$1.06 \cdot 10^{-2}$	45.7
3.16	0.0186	5.3	$1.75 \cdot 10^{-2}$	75.7
4.74	0.0279	7.5	$2.48 \cdot 10^{-2}$	107.1
6.32	0.0372	6.3	$2.08 \cdot 10^{-2}$	90.0
7.9	0.0465	5.6	$1.85 \cdot 10^{-2}$	80.0
9.48	0.0558	3.75	$1.24 \cdot 10^{-2}$	53.6
11.06	0.0651	2.95	$9.69 \cdot 10^{-3}$	82.1
12.64	0.0744	1.00	$3.31 \cdot 10^{-3}$	14.3
14.22	0.0837	0.95	$3.14 \cdot 10^{-3}$	13.6
15.8	0.0930	0.80	$2.65 \cdot 10^{-3}$	11.4

Table II

Solubility(s) of spironolactone as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	Dissolved methyltestosterone mg./ml.	moles/lit.	S/S$_o$
0	0	[S$_o$ = 0.06	$1.44 \cdot 10^{-4}$]	1
1.6	0.0104	1.342	$3.23 \cdot 10^{-3}$	22.4
3.2	0.0208	2.288	$5.5 \cdot 10^{-3}$	38.1
4.8	0.0312	2.816	$6.77 \cdot 10^{-3}$	46.9
6.4	0.0416	2.992	$7.19 \cdot 10^{-3}$	49.9
8.0	0.0520	2.99	$7.19 \cdot 10^{-3}$	49.9
9.6	0.0624	2.73	$6.59 \cdot 10^{-3}$	45.5
11.2	0.0728	2.66	$6.40 \cdot 10^{-3}$	44.4
12.8	0.0832	2.62	$6.29 \cdot 10^{-3}$	43.6
14.4	0.0936	2.82	$6.77 \cdot 10^{-3}$	46.9
16.0	0.104	2.00	$4.81 \cdot 10^{-3}$	33.4

Table III

The solubility/s of pregnenetriolone-triacetate [=prolac] as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	Dissolved prolac mg./ml.	moles/lit.	S/S$_o$
0	0	[S$_o$ = 0.010	$2.1 \cdot 10^{-5}$]	1
0.5	0.00295	0.036	$7.59 \cdot 10^{-5}$	3.6
1.0	0.0059	0.047	$9.92 \cdot 10^{-5}$	4.7
2.0	0.0118	0.061	$1.29 \cdot 10^{-4}$	6.1
5.0	0.0295	0.154	$3.25 \cdot 10^{-4}$	15.4
10.0	0.0590	0.227	$4.79 \cdot 10^{-4}$	22.7
15.0	0.0885	0.291	$6.14 \cdot 10^{-4}$	29.1
20.0	0.1180	0.280	$5.9 \cdot 10^{-4}$	28.0

Table IV
Solubility/s of hydrocortisone as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	Dissolved hydrocortisone mg./ml.	moles/lit.	S/S$_o$
0	0	[S$_o$ = 0.36	9.9 $\cdot 10^{-4}$]	1
1.59	9.38 $\cdot 10^{-3}$	3.25	8.97 $\cdot 10^{-3}$	9.06
3.18	1.88 $\cdot 10^{-2}$	5.14	1.42 $\cdot 10^{-2}$	14.34
4.77	2.81 $\cdot 10^{-2}$	4.78	1.32 $\cdot 10^{-2}$	13.33
6.36	3.75 $\cdot 10^{-2}$	3.65	1.01 $\cdot 10^{-2}$	10.20
7.95	4.70 $\cdot 10^{-2}$	3.30	9.10 $\cdot 10^{-3}$	9.19
9.54	5.63 $\cdot 10^{-2}$	4.00	1.1 $\cdot 10^{-2}$	11.11
11.13	6.57 $\cdot 10^{-2}$	3.20	1.16 $\cdot 10^{-2}$	11.72
12.72	7.51 $\cdot 10^{-2}$	3.20	8.83 $\cdot 10^{-3}$	8.92
14.31	8.45 $\cdot 10^{-2}$	2.22	6.12 $\cdot 10^{-3}$	6.18
15.9	9.38 $\cdot 10^{-2}$	2.00	5.52 $\cdot 10^{-3}$	5.59

Table V
Solubility/s of prednisolone as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	dissolved prednisolone mg./ml.	moles/lit.	S/S$_o$
0	0	[S$_o$ = 0.610	1.7 $\cdot 10^{-3}$]	1
1.29	9.95 $\cdot 10^{-3}$	3.18	8.82 $\cdot 10^{-3}$	5.19
2.57	1.98 $\cdot 10^{-2}$	5.54	1.54 $\cdot 10^{-2}$	9.06
3.86	2.98 $\cdot 10^{-2}$	8.23	2.28 $\cdot 10^{-2}$	13.41
5.15	3.97 $\cdot 10^{-2}$	5.62	1.56 $\cdot 10^{-2}$	9.18
6.43	4.96 $\cdot 10^{-2}$	5.33	1.48 $\cdot 10^{-2}$	8.71
7.72	5.96 $\cdot 10^{-2}$	5.38	1.49 $\cdot 10^{-2}$	8.76
9.00	6.94 $\cdot 10^{-2}$	4.81	1.34 $\cdot 10^{-2}$	7.88
10.30	7.95 $\cdot 10^{-2}$	4.45	1.23 $\cdot 10^{-2}$	7.24
11.58	8.94 $\cdot 10^{-2}$	4.22	1.17 $\cdot 10^{-2}$	6.88
12.9	9.95 $\cdot 10^{-2}$	4.02	1.11 $\cdot 10^{-2}$	6.53

Table VI
Solubility/s of dexamethasone as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	Dissolved dexamethasone mg./ml.	moles/lit.	S/S$_o$
0	0	[S$_o$ = 0.11	3.43 $\cdot 10^{-4}$]	1
1.275	9.84 $\cdot 10^{-3}$	2.88	7.33 $\cdot 10^{-3}$	26.2
2.55	1.97 $\cdot 10^{-2}$	4.97	1.27 $\cdot 10^{-2}$	45.2
3.825	2.95 $\cdot 10^{-2}$	5.99	1.52 $\cdot 10^{-2}$	54.5
6.375	4.92 $\cdot 10^{-2}$	4.91	1.25 $\cdot 10^{-2}$	44.6
7.65	5.90 $\cdot 10^{-2}$	4.40	1.12 $\cdot 10^{-2}$	40.0
8.925	6.89 $\cdot 10^{-2}$	5.46	1.39 $\cdot 10^{-2}$	49.6
10.20	7.87 $\cdot 10^{-2}$	6.40	1.63 $\cdot 10^{-2}$	58.2
11.475	8.85 $\cdot 10^{-2}$	6.05	1.54 $\cdot 10^{-2}$	55.0
12.75	9.84 $\cdot 10^{-2}$	5.06	1.29 $\cdot 10^{-2}$	46.0

Table VII
The solubility/s of triamoinolone base as a function of γ-cyclodextrin concentration

γ-cyclodextrin concentration %	moles/lit.	Dissolved triamcinolone base mg./ml.	moles/lit.	S/S_o
0	0	[S_o = 0.21	$4.8 \cdot 10^{-4}$]	1
1.32	$1.02 \cdot 10^{-2}$	3.05	7.10^{-3}	14.5
2.65	$2.04 \cdot 10^{-2}$	5.56	$1.28 \cdot 10^{-2}$	26.5
3.97	$3.06 \cdot 10^{-2}$	8.25	$1.90 \cdot 10^{-2}$	39.3
5.30	$4.08 \cdot 10^{-2}$	10.25	$2.36 \cdot 10^{-2}$	48.8
6.62	$5.10 \cdot 10^{-2}$	12.44	$2.86 \cdot 10^{-2}$	59.2
7.94	$6.12 \cdot 10^{-2}$	13.44	$3.09 \cdot 10^{-2}$	64.0
9.27	$7.14 \cdot 10^{-2}$	13.50	$3.11 \cdot 10^{-2}$	64.3
10.59	$8.16 \cdot 10^{-2}$	13.69	$3.15 \cdot 10^{-2}$	65.2
11.91	$9.18 \cdot 10^{-2}$	14.63	$3.37 \cdot 10^{-2}$	69.7
13.23	$1.02 \cdot 10^{-1}$	12.06	$2.78 \cdot 10^{-2}$	57.4

Table VIII
The solubility/s of various steroids in a 10% aqueous γ-cyclodextrin solution

	In distilled water		In γ-cyclodextrin solution		S/S_o
	mg./ml.	moles/lit.	mg./ml.	moles/lit.	
spironolactone	0.06	$1.44 \cdot 10^{-4}$	2.7	$6.5 \cdot 10^{-3}$	45
nortestosterone	0.31	$1.13 \cdot 10^{-3}$	1.06	$3.87 \cdot 10^{-3}$	3.4
methyltestosterone	0.07	$2.35 \cdot 10^{-4}$	1.4	$4.6 \cdot 10^{-3}$	19.7
androst - 4 - en - 3, 17 - dione	0.08	$2.86 \cdot 10^{-4}$	0.63	$2.2 \cdot 10^{-3}$	7.6
progesterone	0.016	$5.1 \cdot 10^{-5}$	0.095	$3.0 \cdot 10^{-4}$	5.9
Reichstein S	0.06	$1.7 \cdot 10^{-4}$	2.01	$5.8 \cdot 10^{-3}$	33.5
Reichstein S - 17 - acetate	0.11	$2.9 \cdot 10^{-4}$	2.4	$6.2 \cdot 10^{-3}$	21.5
16 - α - methyl - Reichstein S	0.011	$3.1 \cdot 10^{-5}$	0.73	$2 \cdot 10^{-3}$	66.3
hydrocortisone	0.36	$9.9 \cdot 10^{-4}$	4.3	$1.2 \cdot 10^{-2}$	11.9
monac	0.008	$2.0 \cdot 10^{-5}$	0.23	$6.1 \cdot 10^{-4}$	28.8
prolac	0.01	$2.1 \cdot 10^{-5}$	0.25	$5.3 \cdot 10^{-4}$	25.0
oestrone	0.03	$1.1 \cdot 10^{-4}$	0.355	$1.31 \cdot 10^{-3}$	11.8
methyl-secodione	0.057	$1.9 \cdot 10^{-4}$	0.2	$6.6 \cdot 10^{-4}$	3.5
dexamethasone	0.11	$3.43 \cdot 10^{-4}$	6.0	$1.53 \cdot 10^{-2}$	54.5
prednisolone	0.61	$1.7 \cdot 10^{-3}$	4.6	$1.28 \cdot 10^{-2}$	7.54
triamcinolone base	0.21	$4.8 \cdot 10^{-4}$	13.6	$3.13 \cdot 10^{-2}$	64.8

Example 2
The preparation of a spironolactone - γ - cyclodextrin complex [molar ratio: 1:2]

1531 mg. [1.03×10^{-3} moles] of γ-cyclodextrin containing altogether 15% crystal and included water are dissolved in 4 ml. of water at 60°C. 213 mg. [5.1×10^{-4} moles] of spironolactone are separately dissolved in 4 ml. of a 96% ethanol at 60°C. The two solutions are slowly admixed under continuous stirring. In a short time the precipitation of the crystalline complex can be observed. The mixture is cooled to room temperature under vigorous stirring for 3 hours, whereupon it is kept at about 0°C for 12 hours. The crystalline product is filtered off and dried. 1476 mg. of the title complex are obtained containing 12% of spironolactone.

According to thermoanalytical measurements the product is an inclusion complex. This is supported also by the X-ray diffraction examinations, since on the diffractogram of the product intensive reflection peaks are observed at an angle of 2 ⌀, which is completely different from the results obtained with physical mixture.

Preparation of a complex with a molar ratio of 1:3

1539 mg. [1.03×10^{-3} moles] of γ-cyclodextrin containing 15% of water are dissolved in 4 ml. of water at 60°C. 140 mg. [3.34×10^{-4} moles] of spironolactone are separately dissolved in 4 ml. of a 96% ethanol at 60°C. The two solutions are admixed as described hereinabove, stirred, cooled and filtered. 1342 mg. of a complex containing 8.25% of spironolactone are obtained. According to thermoanalytical measurements the product is an inclusion complex. About 79.3% of the steroid added to the reaction mixture is isolated as a complex. A complex with a molar ratio of 1:3 should theoretically contain 9.7% of spironolactone.

Attempt to prepare a complex with a molar ratio of 1:1

660 mg. [4.43×10^{-4} moles] of γ-cyclodextrin hav-

ing 15% water are dissolved in 5 ml. of water at 60°C. 200 mg. [4.8×10^{-4} moles] of spironolactone are separately dissolved in 5 ml. of a 96% ethanol having a temperature of 60°C. The two solutions are admixed as described above, stirred, filtered and dried. 643.2 mg. of a product containing 22.7% of spironolactone are obtained. A 1:1 complex should theoretically contain 24.3% of spironolactone. The solid product contains only 69% of the steroid added to the reaction mixture and according to the thermoanalytical measurements a substantial amount of the spironolactone is present as a simple, physical mixture, i.e. in uncomplexed form.

Preparation of a 1:2 spironolactone - γ - cyclodextrin complex by kneading in a 50% ethanolic medium

1486 mg. [9.8×10^{-4} moles] of γ-cyclodextrin having a humidity of 15% and 203 mg. [4.9×10^{-4} moles] of spironolactone are thoroughly kneaded with 2 ml. of a 50% ethanol. During this procedure the evaporation loss is restored by adding 1 ml. of a 50% ethanol. The product is dried in an desiccator of 60°C. A homogenous complex containing 13.55% of active ingredient [theoretical: 13.85%] is obtained. The material loss is minimal.

To prove the formation of cyclodextrin inclusion complexes with thermoanalytical methods can generally be employed with good results. In case of steroids, however, the applicability of these methods is restricted since the decomposition of the steroids and γ-cyclodextrin often takes place in the same temperature range. In the case of spironolactone the complex formation is verified also by differential scanning calorimetric studies, since if a physical mixture is present, an endothermic peak characteristic of spironolactone is observed at 203°C, while if a complex is formed this peak is lacking.

In case of the complexes prepared with a 1:2 or 1:3 molar ratio, it can be established that there is no free spironolactone present, but these experiments alone are not sufficient to find out whether in the complexes prepared with a molar ratio of 1:3 free cyclodextrin is present or a complex with a different crystalline structure is formed.

The dissolution of the steroids is substantially accelerated by the formation of complexes as illustrated by the following experiments.

To compare the dynamic dissolution velocity of spironolactone and a 1:2 spironolactone - γ - cyclodextrin complex 6 mg. of spironolactone and 18.6 mg. of the γ-cyclodextrin complex were added to 50 ml. of distilled water having a constant temperature of 25.0°C. The γ-cyclodextrin complex contained 12% of active ingredient. Under continuous stirring samples were taken, filtered and the concentration of dissolved spironolactone was determined by u.v. photometric measurements. During the experiments the free steroid was added to the system in an amount exceeding the water-solubility limit, while the amount of the complex was selected so that at a total dissolution of the dissolved active ingredient the concentration equals to the dissolution limit determined for the free steroid. The results are shown in Table IX.

Table IX

Velocity of the dissolution of free spironolactone and spironolactone - γ - cyclodextrin complex at 25°C

Time [min]	Concentration of dissolved spironolactone [μg/ml.]	
	Spironolactone	complex
1	8	30
3	14	43 } limit of value
5	20	43 } at 3 min.
10	30	44
15	35	43
20	39	44
30	42 } limit value at	44
60	44 } 30-60 min.	43

Example 3

The preparation of prednisolone - γ - cyclodextrin complex [molar ratio: 1:2]

1550 mg. [1.02×10^{-3} moles] of γ-cyclodextrin containing 15% of humidity are dissolved in 5 ml. of distilled water at 60°C. The solution is admixed with 185 mg. [5.1×10^{-4} moles] of prednisolone in 5 ml. of a 96% ethanol of 60°C. The mixture is slowly cooled under continuous stirring. To complete crystallization the mixture is kept in a refrigerator for 12 hours. The product is filtered off and dried in an desiccator at 80°C. 1366 mg. of a complex are obtained containing 11.2% of active ingredient. [Calculated active ingredient concentration for a 1:2 complex: 12.2%]. 82.7% of the prednisolone present in the reaction mixture is included in the complex.

The differential thermogravimetrical spectrum of the product shows only a small peak at 278°C [e.g. the material loss is low], while in the corresponding spectrum of a physical mixture having the same active ingredient concentration a high peak is present at the same temperature indicating the decomposition of the steroid. The same conclusions can be drawn from the thermal evolution analysis [TEA] curves. From the complex nly a small amount of decomposition product is evolved at 285°C, while in the case of a mechanical mixture a high peak can be observed at 285°C also on this curve. The differential

scanning calorimetric [DSC] curve of the physical mixture shows a high exothermic peak at 243°C which can be explained by the oxidation of prednisolone. On the DSC curve of the complex only a small effect can be observed at the same temperature. The complex character of the crystalline product was confirmed also by the X-ray diffraction measurements.

The velocity of the dissolution of 30 mg. of prednisolone and 188 mg. of a γ-cyclodextrin complex thereof containing 11.2% of active ingredient [molar ratio: 1:2] was tested as described in Example 2. The results are set forth in Table X.

Table X

Velocity of the dissolution of prednisolone and prednisolone - γ - cyclodextrin complex at 25°C

Time [min.]	Concentration of dissolved prednisolone [μg/ml]	
	prednisolone	complex
1	39	350
3	130	400 } limit value at
5	170	413 } at 3-5 min.
10	260	410
15	300	407
30	340	414
60	380 } limit value at	410
90	417 } 90 min.	414

Example 4

Preparation of a 1:2 complex of dexamethasone with γ-cyclodextrin

Following the procedure described in Example 3 from 1496 mg. [9.8×10^{-4} moles] of γ - cyclodextrin containing 15% of water and 196 mg. [4.9×10^{-4} moles] of dexamethasone 1388 mg. of an inclusion complex were prepared containing 10.6% of active ingredient. [Calculated value for a 1:2 complex: 13.1%]. Yield for dexamethasone: 75%.

A 1:2 dexamethasone - γ - cyclodextrin complex can be prepared also by liophilization. 104 mg [2.65×10^{-4} moles] of dexamethasone and 912 mg. [6.1×10^{-4} moles] of γ-cyclodextrin [humidity: 13.6%] are dissolved in 40 ml. of a 50% ethanol solution at room temperature. The cloudy solution is filtered through a glass filter and is subsequently liophilized. The product contains 11.5% of active ingredient. Yield: practically 100%. When heating at 250 to 290°C a substantially lower amount of organic substance is eliminated from the product than from a physical mixture having the same active ingredient concentration and the pure dexamethasone, respectively. From this one can conclude that the overwhelming majority of dexamethasone is present as a complex.

The velocity of the dissolution of 7.6 mg. of dexamethasone, 47.3 mg. of a complex containing 10.6% of active ingredient and 43.3 mg. of a liophilized complex containing 11.5% of active ingredient, was examined as described in Example 2. The results are shown in Table XI.

Table XI

Velocity of the dissolution of free dexamethasone and a dexamethasone - γ - cyclodextrin complex in water, at 25°C

Time [min]	Concentration of dissolved dexamethasone [μg/ml]		
	dexamethasone	complex	liophilized complex
1	21	107 } limit value	103 } limit value
3	44	111 } at 1 min.	100 } at 1 min.
5	52	105	105
10	83	108	103
20	85	106	106
30	95	105	103
45	99 } limit after	109	104
90	104 } 90 min.	103	105

Example 5

Preparation of a 1:2 complex of methyltestosterone with γ-cyclodextrin

Following the procedure described in Example 3, starting from 1497 mg. [10^{-3} moles] of methyltestosterone 1270 mg. of a complex containing 10.1% of

active ingredient [calculated value: 10.45%] are obtained. Yield calculated for methyltestosterone: 81%.

The velocity of the dissolution of 7 mg. of methyltestosterone and 35.2 mg. of a complex containing 10.1% of active ingredient was examined as described in Example 2. The results are shown in Table XII.

Table XII

Velocity of the dissolution of free methyltestosterone and the γ-cyclodextrin complex thereof in water at 25°C

Time	Concentration of dissolved methyltestosterone [μg/ml]	
	methyltestosterone	complex
1	9	52 } limit value after
3	15	70 } 3 min.
5	20	68
10	25	72
20	40	71
30	51	72
45	65 } limit value after	69
60	71 } 60 min.	71

Example 6

Preparation of a 1:2 complex of hydrocortisone with γ-cyclodextrin

Following the procedure described in Example 3 from 1514 mg. [1.01 x 10^{-3} moles] of γ-cyclodextrin containing 13.6% of humidity and 185 mg. [5.1 x 10^{-4} moles] of hydrocortisone 1311 mg. of a complex containing 11.8% of active ingredient [calculated: 12.3%] are prepared. Yield calculated for hydrocortisone: 83.7%.

The velocity of the dissolution of 28 mg. of hydrocortisone and 151 lmg. of a complex containing 11.8% of active ingredient was determined as described in Example 2. The results are shown in Table XIII.

Table XIII

Velocity of the dissolution of free hydrocortisone and a γ-cyclodextrin complex thereof in water, at 25°C

Time [min.]	Concentration of dissolved hydrocortisone [μg/ml]	
	hydrocortisone	complex
1	33	304 } limit value at
3	80	352 } 3 min.
5	123	359
10	197	360
20	264	355
30	305	358
45	331 } limit value at	354
60	357 } 60 min.	359

The formation of complexes was verified also by a simple qualitative method. In 100 ml. glasses 50-50 ml. of distilled water were filled and placed on black paper. On the surface of the water 3 mg. of steroid, 30 mg. of a steroid - γ - cyclodextrin complex, and a physical mixture having the same active ingredient concentration, respectively were sprinkled. The free steroid floats on the surface of the water showing its hydrophobic character and remains on the surface as a white layer even after a strong shaking. The physical mixture essentially shows the same character as the free steroid. The complex tested sinks down to the bottom of the glass in about 3 to 5 seconds and disintegrates there or disintegration takes place already on the surface of water. The dissolution can be accelerated and completed by a slight movement of the glass. The significant difference was observed in the case of every complex prepared according to Examples 2 to 11.

Example 7

Preparation of a 1:2 complex of progesterone with γ-cyclodextrin

Following the procedure described in Example 7 from 1532 mg. [102 x 10^{-3} moles] of γ-cyclodextrin and 158 mg. [5.04 x 10^{-4} moles] of progesterone 1220 mg. of a complex containing 10.2% of active

ingredient [calculated: 10.82%] are obtained. Yield calculated for progesterone: 78.7%.

Example 8

Preparation of a 1:2 complex of nortestosterone with γ-cyclodextrin

Following the procedure described in Example 3 starting from 1493 mg. [9.95×10^{-4} moles] of γ-cyclodextrin containing 13.6% of water and 136 mg. [4.95×10^{-4} moles] of nortestosterone 1307 mg. of a complex containing 9.2% of active ingredient [calculated: 9.57%] are obtained. Yield calculated for nortestosterone: 88.4%.

Example 9

Preparation of a 1:2 complex of oestrone with γ-cyclodextrin

Following the procedure described in Example 3 starting from 1504 mg. [10^{-3} moles] of γ-cyclodextrin containing 13.6% water and 130 mg. [4.8×10^{-4} moles] of oestrone 1190 mg. of a complex containing 9.25% of active ingredient [calculated: 9.45%] are obtained. Yield for oestrone: 84.7%.

Example 10

Preparation of a 1:2 complex of triamcinolone base with γ-cyclodextrin

Following the procedure described in Example 3 starting from 1498 mg. [9.97×10^{-4} moles] of γ-cyclodextrin having a water content of 13.6% and 213 mg. [4.9×10^{-4} moles] of triamcinolone base 1247 mg. of a complex containing 13.9% of active ingredient are obtained [calculated: 14.39%]. Yield calculated for the triamcinolone base: 81.4%.

Example 11

Preparation of a 1:2 complex of pregnenetriolone triacetate

Following the procedure described in Example 3 but using 8 ml. of distilled water and 8 ml. of a 96% ethanol from 1520 mg. [1.01×10^{-3} moles] of γ-cyclodextrin and 232 mg. [4.9×10^{-4} moles] of pregnenetriolone triacetate 1173 mg of a complex containing 15.1% of active ingredient [calculated: 15.46%] are obtained. Yield calculated for the steroid: 76.3%.

Example 12

Comparison of the effect of α- and γ-cyclodextrin on the solubility of steroids in water

Into aqueous α- and γ-cyclodextrin solutions having the same concentration [7.5×10^{-2} moles/lit] solid steroids were added in a large excess. As soon as the dissolution equilibrium was established, the total steroid concentration of the solution phase was determined. Since starting from β-cyclodextrin such concentrated solutions [10%] cannot be prepared, for β-cyclodextrin we could not give any comparative data.

It had been observed that γ-cyclodextrin had a considerably higher solubility-increasing effect than α-cyclodextrin. The results are shown in Table XIV.

Table XIV

Steroid	Solubility				
	water mg./ml. [S_0]	$7.7.10^{-2}$ mol. α-CD solv. mg./ml. [S_α]	S_α/S_0	γ-CD solv. mg./ml. [S_γ]	S_γ/S_0
methyltestosterone	0.071	0.430	6.06	1.400	19.7
Reichstein-S	0.060	0.675	11.2	2.010	33.5
Reichstein - S- 17 acetate	0.111	0.930	8.4	2.400	21.5
16 - α - methyl - Reichstein - S	0.011	0.330	30	0.730	66.3
monac	0.008	0.076	9.5	0.230	28.8
prolac	0.010	0.080	8	0.250	25.0
oestrone	0.030	0.065	2.2	0.355	11.8
methylsecodione	0.057	0.114	2.0	0.200	3.5

Example 13

Comparative study of the solubility of the complexes of the same steroids with different cyclodextrins

The complexes of progesterone, methyltestosterone and triamcinolone acetonide with α-, β- and γ-cyclodextrin, respectively were prepared following the conventional methods outlined hereinabove. The complexes precipitating from an 50% homogeneous hot ethanolic solution upon cooling were filtered off, dried and the active ingredient concentrations and compositions were determined. The solubility of the complexes was examined in distilled water at 37°C [Table XV].

An equilibrium dissolution was achieved in about 2 to 5 minutes. For these test samples containing 10 mg. of active ingredient/ml. were used. The results show that for all three steroids the γ-cyclodextrin complexes has the highest solubility.

Table XV

steroid	solubility of steroids at 37°C [mg./ml.]	complex	α-CD	β-CD complex	γ-CD
progesterone	0.025	active ingredient content stochiometry solubility [mg. activ ingr./ml.]	14.9% 1:1.58 0.08	10.62% 1:2.08 0.051	12.22% 1:1.51 0.473
methyltestosterone	0.074	active ingredient content stochiometry solubility [mg. active ingr./ml.]	12.8% 1:2.32 0.197	9.42% 1:2.25 0.129	7.8% 1:2.28 1.16
triamcinolone acetonide	0.034	active ingredient content stochiometry solubility [mg. active ingr./ml.]	19.46% 1:1.64 0.156	13.93% 1:2.10 0.962	10.76% 1:2.26 4.174

Example 14

Use of inclusion complexes of steroids with γ-cyclodextrin in pharmaceutical preparations

The steroid-γ-cyclodextrin inclusion complexes according to the invention can be converted into pharmaceutical compositions by the conventional methods of the preparation of pharmaceuticals. In the followings the preparation of certain tablets, ointments and injections is illustrated.

25-mg. spironolactone tablets

Composition:

200 mg. of spironolactone - γ - cyclodextrin complex
60 mg. of lactose
29 mg. of potato starch
9 mg. of talc
2 mg. of magnesium stearate pro tablet

The quantity of spironolactone - γ - cyclodextrin complex relates to a spironolactone content of 12.5%.

Total weight of a tablet: 300 mg.

The tablets are prepared by the conventional dry granulation technique.

10-mg. hydrocortisone tablets

Composition:

85 mg. of hydrocortisone - γ - cyclodextrin complex
20 mg. of carboxymethyl starch
135 mg. of microcrystalline cellulose
3 mg. of stearic acid
7 mg. of talc pro tablet

The quantity of the hydrocortisone - γ - cyclodextrin complex relates to a hydrocortisone content of 11.8%.

Total weight of a tablet: 250 mg.

1.5-mg. oestrone tablets

Composition:

16 mg. of oestrone - γ - cyclodextrin complex
120 mg. of microcrystalline cellulose
34 mg. of starch
3 mg. of stearic acid
2 mg. of colloidal silicic acid
5 mg. of vinylpyrrolidine and vinylacetate copolimerisate pro tablet.

The quantity of the oestrone - γ - cyclodextrin complex relates to an oestrone content of 9.3%.

Total weight of a tablet: 180 mg.

The tablets are prepared in a conventional way by direct pressing.

5-mg. prednisolone tablets

Composition:

45 mg. of prednisolone - γ - cyclodextrin complex
120 mg. of microcyrstalline cellulose
31.5 mg. of starch
1.5 mg. of colloidal silicic acid
2 mg. of magnesium stearate pro tablet

The quantity of the prednisolone - γ - cyclodextrin complex relates to a prednisolone content of 11.2%.

Total weight of a tablet: 200 mg.

The tablets are prepared in a conventional manner.

0.5% prednisolone ointment

To 4.777 g. of Unguentum simplex ointment containing 6% of lanalcohol, 3% of cetylstearyl alcohol and 12% white vaseline (RTM) 223 mg. of a prednisolone - γ - cyclodextrin complex are added. The quantity of the complex relates to a prednisolone content of 11.2%.

1% hydrocortisone ointment

To 4.576 g. of Unguentum simplex ointment 424 mg. of hydrocortisone - γ - cyclodextrin complex are admixed. The quantity of the complex relates to a hydrocortisone content of 11.8%.

0.5% hydrocortisone eye ointment

To 4.778 g. of Oculentum simplex ointment containing 5% of lanacol, 25% of liquid paraffin and 70% of ophthalmologic vaseline 10 mg, of chloramphenicol and 121 mg. of hydrocortison - γ - cyclodextrin complex are added. The quantity of the complex relates to a hydrocortisone content of 11.8%.

5-mg. dexamethasone aqueous injection

Composition:

Dexamethasone - γ - cyclodextrin complex	47.2 mg.
sodium chloride	21 mg.
distilled water in injection quality ad	3 ml.

The complex contains 10.6% of dexamethasone.

Sodium chloride and the dexamethasone - γ - cyclodextrin complex are dissolved in freshly distilled water of injection quality. The solution is made up with water to the desired volume, filtered and filled in ampoules. Sterilization is carried out by autoclave at 120°C for 20 minutes.

CLAIMS

1. Inclusion complexes of steroids poorly soluble in water with γ-cyclodextrin.

2. Inclusion complexes as claimed in claim 1 wherein the steroid is selected from:
methyltestosterone
spironolactone,
pregnenetriolone triacetate
hydrocortisone
prednisolone,
dexamethasone,
triamcinolone.

3. Inclusion complexes as claimed in claim 1 or claim 2, wherein the steroid: γ-cyclodextrin molar ratio is in the range 1:2 to 1:3.

4. A spironolactone - γ - cyclodextrin inclusion complex having a molar ratio of 1:2.

5. Inclusion complexes as claimed in any preceding claim as herein specifically described.

6. Inclusion complexes as claimed in any preceding claim as herein specifically described in any of Examples 1 to 13.

7. A process for the preparation of inclusion complexes as claimed in any preceding claim, which comprises admixing a solution of the steroid in a C_{1-3} alkanol, ether or acetone with an aqueous solution of γ-cyclodextrin at a temperature between room temperature and the boiling point of the solvent employed, and subsequently cooling the mixture thus obtained and isolating the precipitated steroid - γ - cyclodextrin complex.

8. A process as claimed in claim 7 wherein the steroid and γ-cyclodextrin are used in a molar ratio in the range 1:1 to 1:10 (steroid : γ-cyclodextrin).

9. A process as claimed in claim 7 or claim 8 wherein the steroid and γ-cyclodextrin are used in a molar ratio in the range 1:2 to 1:3 (steroid : γ-cyclodextrin).

10. A process as claimed in any one of claims 7 to 9 substantially as herein described.

11. A process as claimed in any one of claims 7 to 10 substantially as herein described in any one of Examples 1 to 13.

12. Pharmaceutical compositions containing steroids, comprising as active ingredient a inclusion complex as claimed in claim 1 in association with one or more conventional pharmaceutical carriers or excipients, optionally together with one or more further additives.

13. Pharmaceutical compositions as claimed in claim 12 when in a form suitable for parenteral administration.

14. Pharmaceutical compositions as claimed in claim 12, when in a form suitable for oral or local administration.

15. Pharmaceutical composition as claimed in claim 12 substantially as herein described.

16. Pharmaceutical composition as claimed in claim 12 substantially as herein described in Example 14.

17. A process for the preparation of injectable pharmaceutical compositions as claimed in claim 13 wherein the steroid is admixed with a 1 to 10% by weight aqueous solution of γ-cyclodextrin.

18. A process as claimed in claim 17 wherein a 3 to 5% by weight aqueous solution of γ-cyclodextrin is used.

19. A process as claimed in claim 17 or claim 18 for the preparation of pharmaceutical compositions substantially as herein described.

20. Inclusion complexes as claimed in claim 1 when prepared by a process as claimed in claim 7.

21. Inclusion complexes in claim 1 for use in a method of treatment of patients by administering to the said patient one or more steroids poorly soluble in water.

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